

**UNITED STATES AIR FORCE  
ARMSTRONG LABORATORY**

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**Oral Bioavailability of TPH  
and Other Chemicals in Soil:  
Experimental Issues and Risk  
Assessment Applications**

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The experiments reported herein were conducted according to the "Guide for the Care and Use of Laboratory Animals," Institute of Laboratory Animal Resources, National Research Council.

This report has been reviewed by the Office of Public Affairs (PA) and is releasable to the National Technical Information Service (NTIS). At NTIS, it will be available to the general public, including foreign nations.

This technical report has been reviewed and is approved for publication.

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## PREFACE

The purpose of this technical report is to provide a review of the information available on mammalian studies that used soil ingestion as the dosing route. This analysis was conducted in preparation for soil dosing experiments scheduled to be performed by Tri-Service Toxicology in conjunction with the Total Petroleum Hydrocarbon project group. The literature review was performed during the period of May through August, 1995. The work was carried out through contracts with Operational Technologies Corporation and ManTech Environmental Technologies, Inc.

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## INTRODUCTION

The clean-up of Total Petroleum Hydrocarbon (TPH) contaminated soil at Air Force bases nationwide is a major and costly environmental concern. To protect humans from any adverse health effects of these contaminants in a cost effective manner, efforts to develop new risk-based methods for establishing site-specific cleanup criteria are continuing. These efforts include identification of chemicals present in soil after weathering, development of dose-response values, such as reference doses for noncancer effects, and determination of TPH bioavailability in soils.

The purpose of this report is to provide a review of the information available from mammalian studies that used oral exposure to soil as the dosing method. It focuses on the methods used, the effects of soil on the bioavailability or toxicity of contaminants, and the potential use of bioavailability information generated in such studies, in risk assessments and the development of risk-based clean-up of sites. Due to the limited number of soil dosing studies, this review is not limited to chemical constituents of TPH.

Human exposure to TPH in the soil can occur through several pathways, including ingestion of soil or sediment particles, inhalation of dust particles and dermal absorption. Oral dosing studies are useful for improving the soil ingestion pathways in risk assessments of TPH derived chemicals and therefore were the focus here. The alternate pathways of exposure will not be addressed in this report.

The term bioavailability has been used in various ways by different authors (see Table 1). Generally, bioavailability describes the extent and kinetics of absorption of chemicals into the organism of concern. Once absorbed, the administered compound is available for distribution, metabolism, and excretion. Altering the absorption of a chemical may significantly affect all subsequent pharmacokinetic and pharmacodynamic processes and can result in altered toxicity. While this is a fairly simple description of bioavailability, appropriate implementation is complex when evaluating differences between environmental media.

TABLE 1: BIOAVAILABILITY DEFINITIONS USED IN ORAL SOIL DOSING STUDIES

Reference	Definition
Davis <i>et al.</i> , 1992	"bioavailability is used to describe that portion of the ingested As and Pb that is absorbed into the blood stream"
Freeman <i>et al.</i> , 1992	"Relative percentage bioavailability values were estimated by comparing tissue lead concentrations of the test soil to the standard treatment groups."
Freeman <i>et al.</i> , 1993	"Bioavailability of As after oral administration was defined as the percentage of As excreted in the urine of soil-dosed animals compared to that of animals receiving a single intravenous dose of sodium arsenate."
Freeman <i>et al.</i> , 1994	"Relative percent bioavailability values were estimated by comparing tissue lead concentrations of the groups receiving mining waste lead to the lead acetate groups."
Fries <i>et al.</i> , 1989	"bioavailability is defined as the fraction of an administered compound that is absorbed by an animal where it may be metabolized, stored or excreted"
Griffin & Turck, 1991	"Bioavailability of arsenic for the oral/water and oral/soil mixtures groups was determined based on area under the blood concentration vs. time curve (AUC), using the i.v. group as the comparative standard."
Shu <i>et al.</i> , 1988	"Oral bioavailability is defined as the percentage of an orally administered dose which is absorbed via the gastrointestinal system for distribution and disposition into body organs and tissues."
Umbreit <i>et al.</i> , 1988	"bioavailability was calculated [] for each soil sample representing the level of TCDD to be expected in the liver if absorption was identical to the positive control"

Bioavailability adjustments are necessary for developing risk-based clean-up levels as soil or sediment may impact the dose of the contaminant in many ways. Adsorption of the contaminant to soil commonly decreases the amount available to the human system as compared to exposure to the pure chemical. It is also conceivable that availability of a contaminant in soil may be greater to humans than was the pure compound in laboratory toxicity studies using other exposure vehicles (e.g., corn oil, diet, water) (Magee & Bradley, 1994). The kinetics of uptake from different exposure vehicles may vary, even when the total amount absorbed is similar. Weathering (e.g., aging and exposure to light, water, wind, etc.) is another variable that can alter the chemical contaminant in soil. Particularly for metals, the chemical species present in the soil may be altered even in the absence of biodegradation (e.g., changes in organic ligands, salts, or oxidation state). Biodegradation or alteration by organisms such as bacteria or fungi may change the forms of organic and metal containing

compounds. Finally, contaminated sites frequently contain multiple chemical contaminants, that together may have synergistic or antagonistic effects. Soil dosing studies can be used for identification of site specific problems when multiple contaminants are present.

Several methods may be used to incorporate bioavailability information into risk assessments. These include relatively simple bioavailability adjustment factors (BAFs), physiologically based pharmacokinetic (PBPK) models, and other adjustments to either the exposure dose or the dose-response values (e.g., RfDs). The choice of the appropriate method is typically limited by the amount of data on the many factors that can affect oral bioavailability (e.g., exposure vehicle, chemical species, weathering). Site-specific data is often particularly lacking. In all these methods, the critical issue is to compare bioavailability in the risk assessment pathway with that in the toxicity study used to develop the dose-response value. It is the differences between these two that must be accounted for, not the absolute bioavailability (i.e., is absorption less than 100%?).

Section 2.0 of this report examines the methods employed in several soil dosing studies. These studies were selected from a literature search on Medline and Toxline using the key words "soil\*" and "ingestion". Section 3.0 describes the results of these studies and the impact of soil on bioavailability of the contaminant in question. Finally, Section 4.0 briefly describes the alternatives for use of bioavailability information in risk assessment.

## METHODS USED IN ORAL SOIL DOSING

Oral soil dosing studies may be broken down into three main groups by method of administration: capsule, dosed feed, and gavage. The methods of administration were chosen by the individual researchers based upon the nature of the contaminant tested and the desired frequency of administration.

The species most often used for metabolism and pharmacokinetics studies is the rat; the rat is specified as the species of choice under the Toxic Substances Control Act (ToSCA) and is considered an "acceptable model for human risk assessment" by U.S. EPA (Freeman *et al.*, 1992). However, several studies examined in this report deviated from these guidelines due to specific properties of the contaminant in question. The rabbit was used as the test species in

arsenic studies due to the high background blood levels in rats, making detection of increases in blood levels difficult. Additionally, rabbits and humans both eliminate arsenic rapidly along similar pathways (Freeman *et al.*, 1993). Guinea pigs were used in 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (referred to hereafter as dioxin) studies because they are highly sensitive to these compounds. Rats were also used because aryl hydrocarbon hydroxylase (AHH) induction occurs with very low doses of dioxin (McConnell *et al.*, 1984). Umbreit *et al.* (1988) used C57B/6 mice as the test strain because it is known for its responsiveness to dioxin in acute studies. Given the well known species/strain variability of pharmacokinetics and toxicity, it is desirable to have bioavailability data in the species/strain for which the toxicity information is available.

Soil preparation for oral dosing studies was often very similar but each laboratory used its own slightly different techniques. Frequently the soil was sieved to 2 mm and air-dried. Samples for characterization were separated; commonly evaluated soil characteristics are listed in Table 2. In many studies, the soil was then pulverized or sieved again to allow administration by the chosen method. Turkall *et al.* (1992) and Kadry *et al.* (1991) both reported pulverizing the soil to allow passage through a gavage needle. Freeman *et al.* (1992) found that with adequate sieving of the soil, the resulting particles (less than 250  $\mu\text{m}$ ) represented less than 10% of the natural soil sample. They also observed that during mechanical mixing of the soil into feed, the particle size distribution decreased even further.

Unfortunately, these preparations are as problematic as they are necessary. The smaller soil particles have a higher surface area to mass ratio, potentially allowing for more rapid dissolution of the contaminant in the GI tract than natural soil (Freeman *et al.*, 1992). Conversely, the greater surface area of the finer particles may allow more of the contaminant to adsorb tightly, leaving less contaminant available in the GI tract. Although it is the finer particles that reportedly adhere to children's hands (<100  $\mu\text{m}$ ), and hand to mouth contact is a major contributor to the soil ingestion route, soil dosing with these extremely fine particulates does not completely simulate a natural dose (Freeman *et al.*, 1993).

TABLE 2: SOIL CHARACTERISTICS COMMONLY EVALUATED FOR SOIL DOSING STUDIES<sup>1</sup>

Cation Exchange Capacity
Elemental Concentrations or Mineralogy
Geometric Mean Size and Geometric Standard Deviation or Median Particle Size
% Moisture Content
% Organic Matter
pH
% Sand, Silt, Clay <sup>2</sup>

<sup>1</sup> All characteristics are not evaluated for each study; the characteristics chosen for evaluation are dependent upon the author.

<sup>2</sup> Sand, silt and clay are defined by the USDA. Sand is defined as having grain sizes of 50 to 2000  $\mu\text{m}$ . Silt is defined as having grain sizes of 2 to 50  $\mu\text{m}$ . Clay is defined as having grain sizes of 2  $\mu\text{m}$  or smaller. (Buol *et al.*, 1980)

The amount of soil administered to study animals in the 1993 Freeman *et al.* study exceeded a maximum dose in humans (based upon a pica child). The study animals were administered 2.0 g soil/kg bodyweight; the ingestion rate of soil for a pica child is 0.7 g/kg bodyweight. As a child with pica behavior ingests the entire composition of the soil and not just the finest dust particles, soil dosing studies may be testing the worst case scenario (Johnson *et al.*, 1991). Finally, humans are much larger than the study animals, so it is not clear if the ingestion of equal sized particles would produce identical effects in the gastro-intestinal (GI) tract. Despite all these potential caveats, studies with soil remain critical to better understanding it's impact on chemical bioavailability.

The controls used in soil dosing studies varied widely from author to author. The number and types of controls were dependent on the objective of the study; estimating relative bioavailability was often not the study objective. As a result, BAFs are not derivable from all studies.

Tables 3 through 7 list the details of the methods used in the soil dosing studies examined in this report. The completeness of the table, especially the Dose/Duration and Soil columns, was highly dependent on the completeness of the methods reported. Unless the test substance is indicated as "spiked" in the "Soil" column, the study was performed with a contaminated soil from an actual site. The tables are arranged by administration route; the studies are ordered by author and year.

## Capsule Studies

Capsule administration is used frequently in pharmacological and product testing studies, but was infrequently used in soil dosing studies. Table 3 gives the details of the two capsule studies found in our literature search. Rabbits were used in single dose studies of soil contaminated by arsenic from a smelter. As discussed above, when studying arsenic, rabbits were considered a better model than rats for human comparison (Freeman *et al.*, 1993).

The dissolution time of the gelatin casing is an issue in capsule studies that was not addressed. It is unclear if the capsule itself alters absorption kinetics. Another issue concerning capsule studies is the effect of adding a large dose of dried soil to the digestive tract of the study animal. Freeman *et al.* (1993), noted that the 1.0 gram per kilogram test group experienced a reduced food consumption period during the first two days after dosing. Apparently the largest soil dose caused an irritant effect on the GI tract, producing a delay in emptying time, which in turn limited food intake. This GI tract irritation was not reported in gavage studies when even greater amounts of soil were administered as a slurry or suspension. (See Tables 5 and 6.)

TABLE 3: METHODS SUMMARY FOR CAPSULE STUDIES

Study Animals	Soil Dose/Duration	Soil	Controls	Reference
New Zealand White rabbit, ~2 kg (F)	2.0 g soil/kg bw (1380 mg As/kg soil & 3900 mg Pb/kg soil); fasted 16 hrs prior, 4 hrs after; 3 to 36 hrs obs.	Air-dried, Sieved (<250 $\mu$ m, median size = 48 $\mu$ m), Blended (5 soils blended to achieve conc.), Encapsulated	No treatment	Davis <i>et al.</i> , 1992.
New Zealand White rabbit, ~2 kg (M&F)	0.2, 0.5, or 1.0 g soil/kg bw (3.9 g As/kg soil); fasted 16 hrs prior, 4 hrs after; 5 days obs.	Preparation not specified (Geometric Mean Size = $19 \pm 23$ $\mu$ m)	1. No treatment 2. Sodium arsenate in water iv 3. Sodium arsenate in water gavage	Freeman <i>et al.</i> , 1993.
bw = body weight; F = female; hrs = hours; M = male; obs. = observation period				

## Dosed Feed Studies

Dosed feed was used in three multiple exposure studies. This method possibly provides a more natural administration route for a soil contaminant as compared to human environmental exposure. The details of these studies are found in Table 4.

The 1992 Freeman *et al.* study used AIN-76 sucrose-free meal in order to avoid diluting the diet with the soil. A full allotment of sucrose was added to the control feed; the soil or lead acetate replaced a portion of the added sucrose in the test feeds. In this way the weight, dryness, nutritional balance and fiber content of the diet was not upset.

An issue that might present itself in dosed feed studies is the palatability of the mixture of feed and soil. Dacre and Ter Haar (1977) reported no significant difference in food consumption between the control diet and the diet with soil. Freeman *et al.* (1972) also observed no palatability problems.

TABLE 4: METHODS SUMMARY FOR DOSED FEED STUDIES

Study Animals	Soil Dose/Duration	Soil	Controls	Reference
Wistar rat, 125-150 g initial bw (M)	2.15 or 5.0% soil in feed (56 or 52 mg Pb/kg soil), <i>ad libitum</i> , 30 or 90 day dose	[Roadside or House paint soil] Finely ground, Mechanically mixed	1. Normal diet 2. Pb acetate in 50% aq. ethanol, sprayed on feed while mixing	Dacre & Ter Haar, 1977.
Sprague-Dawley rat, 7-8 wks old at start (M&F)	0.2, 0.5, 2, or 5% soil in meal (2, 4, 16, 41 or 8, 20, 78, 195 mg Pb/kg soil), <i>ad libitum</i> , 30 day dose	Air-dried, Sieved (<250 $\mu$ m, Geometric Mean Size = $48 \pm 46$ $\mu$ m, or $42 \pm 44$ $\mu$ m), Blended into 2 test soils	1. No treatment (Purified diet) 2. Lead acetate dosed-feed 3. Lead acetate iv	Freeman <i>et al.</i> , 1992. Freeman <i>et al.</i> , 1994.
Sprague-Dawley rat, 400-500 g initial bw (M)	5% soil in meal (insufficient data in text to calculate dose), 5 day dose; 10 day obs.	[Sandy Loam] Air dried, Sieved (2mm), Spiked (PCB in acetone), Stored (-5°C, 8 years), Sieved (125 $\mu$ m)	1. PCB in acetone, in meal 2. PCB in corn oil gavage	Fries <i>et al.</i> , 1989. Fries <i>et al.</i> , 1981.
bw = body weight; F = female; M = male; obs. = observation period				

However, in order to ensure palatability of the feed, soil was added only up to 5% in either study. The actual chemical dose received can be determined by measuring daily food intake.

In designing such studies, it may be important to consider if the amount of soil eaten will provide an adequate dose of chemical to study either bioavailability or toxicity. Dacre and Ter Haar (1977) and Freeman *et al.* (1972) measured the food intake of the study animals; the doses received were comparable with control doses.

### Gavage Studies

For the purpose of this report, the gavage studies have been divided by solution method: suspensions, slurries, and extraction. These studies are detailed in Tables 5 through 7.

Suspensions were identified as soil doses that had been indefinitely suspended in gum acacia. Although not used in any of these studies, methyl cellulose also provides a true suspension. The suspension gavage studies are detailed in Table 5.

TABLE 5: METHODS SUMMARY FOR SUSPENSION GAVAGE STUDIES

Study Animals	Soil Dose/Duration	Soil	Controls	Reference
Sprague-Dawley rat, 275-300 g (M)	500 mg soil/rat (440 g TCE/kg soil, unadjusted for volatilization losses); 96 hrs obs.	[Sandy or Clay soils] Sieved, Pulverized, Spiked & Suspended (150 µl TCE, 500 mg soil, 2.85 ml aqueous 5% gum acacia)	neat TCE gavage (No TCE in gum acacia control)	Kadry <i>et al.</i> , 1991a.
Sprague-Dawley rat, 250-275 g (F)	500 mg soil/rat (440 g TCE/kg soil, unadjusted for volatilization losses); fasted overnight; 72 hrs obs.	[Sandy or Clay soils] Sieved, Pulverized, Spiked & Suspended (150 µl TCE, 500 mg soil, 2.85 ml aqueous 5% gum acacia)	neat TCE gavage (No TCE in gum acacia control)	Kadry <i>et al.</i> , 1991b.
Sprague-Dawley rat, 250-300 g (M)	0.5 g soil/rat (264 g benzene/kg soil, unadjusted for volatilization losses); fasted overnight; 120 min obs.	[Sandy or Clay soils] Pulverized (Particle size 0.05-2.0 mm), Spiked (150 µl benzene/0.5 g soil), Suspended (2.85 ml 5% aq. gum acacia)	Benzene in gum acacia gavage	Turkall <i>et al.</i> , 1988.
Sprague-Dawley rat, 250-300 g (M)	0.5 g soil/rat (260 g toluene/kg soil, unadjusted for volatilization losses); fasted overnight; 180 min obs.	[Sandy or Clay soils] Pulverized, Spiked (150 µl toluene/0.5 g soil), Suspended (2.85 ml 5% gum acacia)	Toluene in gum acacia gavage	Turkall <i>et al.</i> , 1991.



Sprague-Dawley rat (M&F)	0.5 g soil/rat (259 g <i>m</i> -xylene/kg soil, unadjusted for volatilization losses); fasted 18 hrs prior, 2 hrs after; 24 hrs obs.	[Sandy or Clay soils] Pulverized, Spiked (150 µl <i>m</i> -xylene/0.5 g soil), Suspended (2.85 ml 5% gum acacia)	<i>m</i> -xylene in gum acacia gavage	Turkall <i>et al.</i> , 1992.
Guinea pig, 250-280 g initial bw (M&F)	4.1-15.0 ml suspension/guinea pig (0.32, 3, 6, 12 µg dioxin/kg bw)(90-230 ng dioxin/kg soil); 60 day obs.	[Manufacturing plant or Salvage yard soils] Mechanically homogenized, Sifted, Suspended (10% soil in 5% aq. gum acacia)	1. Dioxin in corn oil: acetone gavage 2. Dioxin on cleaned soil in gum acacia gavage 3. Corn oil gavage 4. Cleaned soil in acacia gavage	Umbreit <i>et al.</i> , 1985. Umbreit <i>et al.</i> , 1986a.
Hartley guinea pig, ~225 g initial bw (M&F)	1.3, 3.9, 13 mg soil/kg bw (770 µg dioxin/kg Times Beach soil); 60 day obs.  1.4, 2.3, 4.5 mg soil/kg bw (2200 µg dioxin/kg Newark soil); 60 day obs.	[Times Beach or Newark soils] Suspended (10% soil in 5% aq. gum acacia)	1. Decontaminated Newark soil in acacia gavage 2. Dioxin in corn oil:acetone (9:1) gavage 3. Dioxin spiked Newark decontaminated soil in acacia gavage	Umbreit <i>et al.</i> , 1986b. Umbreit <i>et al.</i> , 1987a. Umbreit <i>et al.</i> , 1988a.
Sprague-Dawley rat (M&F)	13 or 4.5 mg soil/kg bw (770 or 2200 µg dioxin/kg soil), 1 or 4 days; 1 day obs.	[Times Beach or Newark soils] Suspended (10% soil in 5% aq. gum acacia)	1. Decontaminated Newark soil in acacia gavage 2. Dioxin spiked Newark decontaminated soil in acacia gavage	Umbreit <i>et al.</i> , 1987a. Umbreit <i>et al.</i> , 1988a.
C57B/6 mice (F)	<1 ml suspension/mouse-day (9.6 or 1.1 µg dioxin/kg bw-day) (2.05 or 0.23 mg dioxin/kg soil), 3 day/wk, 25 wks	[Manufacturing plant or Salvage yard soils] Protected from light, Suspended (10% soil in 5% aq. gum acacia)	1. Decontaminated soil in gum acacia gavage 2. Dioxin in corn oil:acetone (9:1) gavage 3. Dioxin on decontaminated soil in gum acacia gavage 4. Male mice gavaged with #1, 1d/wk, 25 wks.	Umbreit <i>et al.</i> , 1987b.
C57B/6 mice (M)	<1 ml suspension/mouse-day (9.6 or 1.1 µg dioxin/kg bw-day) (2.05 or 0.23 mg dioxin/kg soil), 1 day/wk, 30 wks	[Manufacturing plant or Salvage yard soils] Protected from light, Suspended (10% soil in 5% aq. gum acacia)	1. Decontaminated soil in gum acacia gavage 2. Dioxin in corn oil:acetone (9:1) gavage 3. Dioxin on decontaminated soil in gum acacia gavage 4. Female mice gavaged with #1, 3 day/wk, 27 wks	Umbreit <i>et al.</i> , 1988b.
bw = body weight; F = female; hrs = hours; M = male; min = minutes; obs. = observation period; TCE = trichloroethylene; wk(s) = week(s)				

Slurries refer to soils mixed in excess water; the resulting mixture is generally administered immediately after blending. These are not suspension gavage studies as the soil in slurries will settle out quickly. Slurry studies are described in Table 6.

TABLE 6: METHODS SUMMARY FOR SLURRY GAVAGE STUDIES

Study Animals	Dose/Duration	Soil	Controls	Reference
Albino rabbit, ~2.6 kg final weight (M)	1-2 g soil/rabbit (81 µg dioxin/kg soil), 7 days; 1 day obs.	Air dried, Sieved (200-400 mesh), Slurried (1-2 g soil/10 ml water)	1. Dioxin in acetone spiked soil, not aged 2. Dioxin in acetone spiked soil, aged 30 days 3. Dioxin in acetone:vegetable oil (1:6) 4. Dioxin in alcohol:water (1:1)	Bonaccorsi <i>et al.</i> , 1984.
Sprague-Dawley rat, 400-500 g (M)	(1 g soil/day)/rat in water gavage (insufficient data in text to calculate dose), 5 days; not fasted; 10 days obs.	[Sandy loam] Spiked, Air dried, Stored (-5°C, 8 years), Sieved (125 µm), Slurried (1 g soil in water)	1. PCB in acetone, in meal 2. PCB in corn oil gavage	Fries <i>et al.</i> , 1989. Fries <i>et al.</i> , 1981.
New Zealand white rabbit, 3.1-4.2 kg	(0.8 or 8.0 mg As/kg bw) Fasted 16 hrs prior, 4 hrs after	[Clay or Sandy loam] Sieved (2 mm), Air dried, Spiked, Slurried (aqueous)	1. Sodium arsenate aqueous iv 2. Sodium arsenate aqueous gavage	Griffin & Turck, 1991.
Sprague-Dawley rat (F)	0.004-1.25 g soil/rat (880 µg dioxin/kg soil); fasted overnight; 6 day obs.	[Minker soil] Sieved (60-gauge), Slurried (distilled water, total vol = 2 ml)	1. Dioxin in corn oil gavage 2. Uncontaminated soil in water gavage 3. Corn oil gavage 4. Water gavage 5. No treatment	Lucier <i>et al.</i> , 1986.
Hartley guinea pigs, 200-220 g (M)	≤3.6 g soil/guinea pig (770 or 880 µg dioxin/kg soil); fasted 24 hrs before; 30 day obs.	[Times Beach or Minker soil] Air-dried, Homogenized, Sifted (6 mm), Sifted (60 gauge), Slurried (≤3.6 g soil /5 ml distilled water)	1. Uncontaminated soil aqueous gavage 2. Dioxin in corn oil gavage 3. Corn oil gavage	McConnell <i>et al.</i> , 1984.
Sprague-Dawley rats (F)	0.01-1.8 g soil/rat (880 µg dioxin/kg soil); 6 day obs.	[Minker soil] Air-dried, Homogenized, Sifted (6 mm), Sifted (60 gauge), Slurried (distilled water)	1. Uncontaminated soil aqueous gavage 2. Dioxin in corn oil gavage 3. Corn oil gavage	McConnell <i>et al.</i> , 1984.

Sprague-Dawley rat, 180-220 g (F)	0.5 ml soil slurry gavage/rat (13, 23 ng dioxin/rat (10-15 hrs storage) or 21, 23 ng dioxin/rat (8 days storage)); fasted overnight, 6 hrs after	Slurried (water), Sieved (160 $\mu$ m), Dried (60°C), Ground in a mortar, Mixed in dioxin & methanol, Evaporated, Stored (10-15 hrs at room temp. or 8 days at 40°C), Slurried (37% w/w in water)	1. Dioxin in ethanol gavage 2. Dioxin in activated carbon aqueous gavage (25% w/w)	Poiger & Schlatter, 1980.
Sprague-Dawley rat, 180-250 g (M)	2 g soil/kg bw (3.5, 18.5, 20, 87.5, 725 ng dioxin/g soil); fasted overnight, 4 hrs after; 24 hrs obs.	Air-dried, Sieved (40-mesh screen), Blended with uncontaminated soil to conc., Slurried (0.25 g soil/ml water)	Dioxin in corn oil gavage	Shu <i>et al.</i> , 1988.
bw = body weight; F = female; hrs = hours; M = male; obs. = observation period; PCB = polychlorinated biphenyls; vol = volume; wk(s) = week(s)				

Table 7 provides information on one gavage study using materials extracted from soil. The extraction method used provided a very complete organic extraction of Love Canal soil. The toxicity of this was compared to the toxicity of the organic phase of Love Canal leachate.

TABLE 7: METHOD SUMMARY FOR ORAL DOSING WITH EXTRACTED MATERIALS

Study Animals	Dose/Duration	Soil	Controls	Reference
Sprague-Dawley rat, ~250 g (M&F)	25, 75, 150 mg extract/kg-day, 10 day (days 6-15 of gestation for females); 5 day obs.	[Love Canal soil extract] 1 kg soil, Extracted (Soxhlet extractor, acetone:hexane (12 hrs), then benzene:methanol (12 hrs)), Vacuum dried, Mixed (5 ml corn oil/kg)	1. Corn oil gavage 2. Organic phase leachate in corn oil gavage	Silkworth <i>et al.</i> , 1986.
F = female; hrs = hours; M - male				

A concern with any aqueous gavage study centers around the question of whether the addition of the soil to the vehicle alters the distribution or form of the chemical. Suspension and slurry studies may not be truly comparable to environmental exposures as the contaminant may have already started dissolving in the gavaging compound before administration to the study animal.

Therefore, it seems most appropriate to mix the chemical with the vehicle and gavage the animals immediately.

Extraction of the contaminant from a soil sample to serve as an exposure dose is poorly comparable to environmental exposure. The extraction in Table 7 is a complete organic extraction; all organics are dissolved and are administered in a form potentially more bioavailable than when present in the soil.

A major problem with the slurry gavage method is the soil remaining in the syringe after dosing may affect the dose administered. As the soil is not bound in a true suspension, particles may cling to the walls of the syringe and gavage tube, making the calculation of the actual dose of soil received somewhat inaccurate.

#### EFFECTS OF SOIL ON BIOAVAILABILITY

Soil dosing theoretically may increase, decrease, or have no effect on the bioavailability of a contaminant. The effect may be dependent not only on the nature of the contaminant but also on the type of soil, how the contaminant came to be in the soil (laboratory spike versus environmental sample), the study animal, and the method of administration. Changes in bioavailability may alter the total amount absorbed and/or the kinetics of absorption. Few studies provide comprehensive data on these aspects although their effects could influence the potential toxicity of the soil exposure.

The results of the studies are presented in table form. In the Test substance column, the soils are actual site-contaminated soils unless identified as a "spiked" sample. The percent bioavailability is shown when available.

### Capsule Studies

The results of the capsule studies are shown in Table 8. Compared to the adsorption from either the intravenous or the oral gavage control, the bioavailability of arsenic in actual site-contaminated soil is decreased.

TABLE 8: RESULTS SUMMARY FOR CAPSULE STUDIES

Test Substance	Results	Bioavailability	Reference
Arsenic or Lead contaminated soil	As: 11% solubilized in small intestine. Pb: 6% solubilized in small intestine.	As: 10% as compared to sodium arsenate (based on blood levels found in 1991 Griffin & Turck study)	Davis <i>et al.</i> , 1992.
Arsenic contaminated soil	Dose dependent delay in urinary & fecal excretion. Decreased food consumption first 24 hours; irritant to gastro-intestinal tract motility.	28% (contaminated soil/sodium arsenate i.v.) 48% (contaminated soil/sodium arsenate gavage)	Freeman <i>et al.</i> , 1993.

### Dosed Feed Studies

The results for the dosed feed studies are found in Table 9. The dosed feed studies dealt with two different contaminants, lead and polychlorinated biphenyls (PCB). The lead contaminated soils showed a decreased bioavailability as compared to a similar dose of lead acetate in the feed.

The Fries *et al.* 1989 study using soils spiked with PCB and stored eight years also showed slightly decreased availability as compared to PCB in a corn oil gavage. It was also noted that in this study, the feed containing PCB contaminated soils showed less bioavailability than the stored soil given by gavage. Apparently, the feed residues bind PCB, allowing less absorption of the contaminant. However, actual PCB bioavailability in this study is uncertain. As the biliary excretion was not measured, no proof is available that the parent compound measured in the feces was really unabsorbed.

TABLE 9: RESULTS SUMMARY FOR DOSED FEED STUDIES

Test Substance	Results	Bioavailability	Reference
Lead contaminated soils	Lower levels of Pb in kidney & bone among rats dosed with soils rather than those given lead acetate in diet. Blood, brain & liver levels were essentially control levels.	Decreased in contaminated soils as compared to lead acetate in diet	Dacre & Ter Haar, 1977.
Lead contaminated soils	Animals fed soils had lower tissue concentrations than those fed diet containing lead acetate.	20%, 9%, 8% (blood, bone, & liver levels, respectively)	Freeman <i>et al.</i> , 1992. Freeman <i>et al.</i> , 1994.
Aged PCB spiked soil	Spiked soil fed in diet was less bioavailable than same spiked soil administered in gavage.	80-90% (spiked soil dose/PCB in corn oil gavage)	Fries <i>et al.</i> , 1989. Fries <i>et al.</i> , 1981.
PCB = polychlorinated biphenyls			

### Gavage Studies

The results from the gavage studies are shown in Tables 10 through 12. Again the studies are divided by solution method. Table 10 features suspension gavage studies. The laboratories of Kadry, Turkall and coworkers used the same test soils (which are known as "sandy" and "clay") spiked with different organic solvents. The Kadry *et al.* (1991a,b) studies with trichloroethylene apparently demonstrated differences in bioavailability related to the two different test soils and the sex of the study animals. Turkall *et al.* (1992) also reported a sex difference in bioavailability.

Several issues arise concerning the studies of Kadry, Turkall and coworkers. First, the concentrations used in these studies were extremely high; the concentrations were well above those typically found at contaminated sites unless a fresh spill had occurred. Second, volatilization of the chemical and determination of the actual administered dose was not reported uniformly. In Turkall *et al.* (1988), much of the benzene was volatilized during suspension; 43, 57 and 61% was lost from the benzene control, the spiked sandy soil and the spiked clay soil, respectively. This loss reduced the actual administered dose to 275, 205 and 190 mg/kg from the benzene control, sandy and clay soils respectively (Travis & Bowers, 1990). Third, the recovery of the chemical and metabolites in the urine, feces, tissues and expired air was highly variable between treatments. The Turkall *et al.* (1988) study with benzene recovered approximately 85, 104 and 63% of the initial dose over the first 48 hours (Travis and

Bowers, 1990). Thus it is unclear if the effects reported are due to altered soil bioavailability or experimental difficulties resulting in inconsistent recoveries. Finally, Travis and Bowers (1990) reevaluated the Turkall study using a physiologically based pharmacokinetic model. Although this approach is a good one, their reliance on an assumed model structure for the GI tract and fitting limited data place their results in the realm of an interesting hypothesis requiring further testing.

The studies of Umbreit and coworkers all showed decreased bioavailability in the contaminated soil as compared to dioxin recontaminated soil (Umbreit *et al.* 1985, 1986a, 1986b, 1987a, 1987b, 1988a). The 1988a study proved dramatically the difference two soils can have on bioavailability. Umbreit *et al.* 1988b study showed increased reproductive toxicity in male C57Bl/6 with the manufacturing site soil as compared to soil recontaminated with dioxin, even though this same contaminated soil had shown decreased bioavailability in rats (Umbreit *et al.* 1985, 1986 & 1988a). No adverse effects were seen with the dioxin recontaminated soil. The earlier study (Umbreit *et al.*, 1987b) performed with female C57B/6 mice showed fewer effects in the dioxin contaminated soil as compared to recontaminated soil and the dioxin in corn oil control. However, even though the manufacturing site soil demonstrated reproductive effects, they were not identical in nature to those in the female mice treated with the dioxin recontaminated soil. Soil analysis showed many other compounds in the site soil, "chlorophenols, phenoxy acids, heavy metals, and polyaromatic carcinogens, including benzo(a)pyrene and benzo(a)anthracene" (Umbreit *et al.*, 1988), that may have contributed to the toxicity.

The slurry gavage studies are found in Table 11. The Bonaccorsi *et al.* (1984) study used rabbits to compare the effects of dioxin in contaminated, spiked and aged spiked soils. Although the aged spiked and spiked soils decreased the bioavailability of dioxin to 56-71%, the actual contaminated soil decreased bioavailability to 32%. The contaminated soil is nearly twice as effective in reducing toxicity as the spiked soils.

TABLE 10: RESULTS SUMMARY FOR SUSPENSION GAVAGE STUDIES

Test Substance	Results	Bioavailability	Reference
TCE spiked soil (Sandy soil) (Male)	Decreased peak plasma concentration. Delayed time to peak plasma concentration. Significantly decreased area under plasma concentration-time curve. (As compared to neat TCE gavage.)	Minor differences were observed but no clear effect on bioavailability was demonstrated.	Kadry <i>et al.</i> , 1991a.
TCE spiked soil (Clay soil) (Male)	Increased peak plasma concentration. Increased absorption $t_{1/2}$ . Delayed time to peak plasma concentration. Significantly increased area under plasma concentration-time curve. (As compared to neat TCE gavage.)	Minor differences were observed but no clear effect on bioavailability was demonstrated.	Kadry <i>et al.</i> , 1991a.
TCE spiked soil (Sandy soil) (Female)	Increased absorption $t_{1/2}$ . Decreased elimination $t_{1/2}$ . (As compared to neat TCE gavage.)	Minor differences were observed but no clear effect on bioavailability was demonstrated.	Kadry <i>et al.</i> , 1991b.
TCE spiked soil (Clay soil) (Female)	Increased maximum plasma levels. (As compared to neat TCE gavage.)	Minor differences were observed but no clear effect on bioavailability was demonstrated.	Kadry <i>et al.</i> , 1991b.
Benzene spiked soil (Sandy soil)	Peak plasma concentration increased. Time to reach peak concentration decreased. (As compared to benzene in gum acacia gavage.)	Minor differences were observed but no clear effect on bioavailability was demonstrated.	Turkall <i>et al.</i> , 1988.
Benzene spiked soil (Clay soil)	Peak plasma concentration increased. Increased area under the plasma concentration-time curve. Decreased elimination $t_{1/2}$ . (As compared to benzene in gum acacia gavage.)	Minor differences were observed but no clear effect on bioavailability was demonstrated.	Turkall <i>et al.</i> , 1988.
Toluene spiked soil (Sandy soil)	Peak plasma concentration decreased; soil altered time course but not amount absorbed. (As compared to toluene in gum acacia gavage.)	Minor differences were observed but no clear effect on bioavailability was demonstrated.	Turkall <i>et al.</i> , 1991.
Toluene spiked soil (Clay soil)	Peak plasma concentration decreased. Decreased elimination $t_{1/2}$ . Soil altered time course but not amount absorbed. (As compared to toluene in gum acacia gavage.)	Minor differences were observed but no clear effect on bioavailability was demonstrated.	Turkall <i>et al.</i> , 1991.
<i>m</i> -xylene spiked soil (Sandy & Clay soil) (Male)	Increased proportion excreted in expired air. (As compared to <i>m</i> -xylene in gum acacia gavage.)	Minor differences were observed but no clear effect on bioavailability was demonstrated.	Turkall <i>et al.</i> , 1992.
<i>m</i> -xylene spiked soil (Female)	<u>Sandy soil</u> -Increased peak plasma concentration. Increased absorption $t_{1/2}$ . Decreased elimination $t_{1/2}$ . Increased area under plasma concentration-time curve. Delayed urinary excretion. (As compared to <i>m</i> -xylene in gum acacia gavage.) <u>Clay soil</u> -Increased absorption $t_{1/2}$ . (As compared to <i>m</i> -xylene in gum acacia gavage.)	Minor differences were observed but no clear effect on bioavailability was demonstrated.	Turkall <i>et al.</i> , 1992.



Dioxin contaminated soils	Slight decrease in weight gain at 4 weeks; recovered at 8 weeks. No other effects. Mortality seen with dioxin recontaminated soil.	Decreased in contaminated soils as compared to recontaminated soil	Umbreit <i>et al.</i> , 1985. Umbreit <i>et al.</i> , 1986a.
Dioxin contaminated soils	Decreased weight gain. No signs of toxicity or dioxin syndrome. Dioxin syndrome & decreased weight gain seen with recontaminated soil.	Decreased in contaminated soils as compared to recontaminated soil	Umbreit <i>et al.</i> , 1986b. Umbreit <i>et al.</i> , 1987a.
Dioxin contaminated soils (rat)	Induction of P-450 and AHH equal for either soil but less than recontaminated soil.	Decreased in contaminated soils as compared to recontaminated soil	Umbreit <i>et al.</i> , 1987a. Umbreit <i>et al.</i> , 1988a.
Dioxin contaminated soils (guinea pig)	Contaminated Newark soil was less bioavailable as compared to recontaminated soil.  Contaminated Times Beach soil was less bioavailable as compared to recontaminated soil.	1.6% (contaminated soil gavage/ recontaminated soil gavage) 29.5% (contaminated soil gavage/ recontaminated soil gavage)	Umbreit <i>et al.</i> , 1988a.
Dioxin contaminated soil (Manufacturing site soil)	Did not produce dioxin syndrome effects. Produced similar number of litters but fewer pups/litter and fewer live pups/litter as compared to decontaminated soil.	Decreased in contaminated soil as compared to dioxin in corn oil gavage and recontaminated soil.	Umbreit <i>et al.</i> , 1987b.
Dioxin contaminated soil (Salvage yard soil)	No effect on reproduction; responses similar to decontaminated soil control.	Not different in contaminated soil as compared to decontaminated soil.	Umbreit <i>et al.</i> , 1987b.
Dioxin contaminated soil (Manufacturing site soil)	Decreased viable litters & pup survival. Dioxin recontaminated soil had no effect.	Increased in contaminated soil as compared to recontaminated soil	Umbreit <i>et al.</i> , 1988b.
Dioxin contaminated soil (Salvage yard soil)	No effect on reproduction. Dioxin recontaminated soil also had no effect.	Not different in contaminated soil as compared to recontaminated soil	Umbreit <i>et al.</i> , 1988b.
AHH = aryl hydrocarbon hydroxylase; TCE = trichloroethylene; $t_{1/2}$ = half-life			

In the 1991 Griffin and Turck study, the presence or type of soil did not effect bioavailability as much as the dose and the sex of the study animal. The results of this study show that the gavage route, with or without soil, decreased bioavailability as compared with the intravenous

route. These results do not appear consistent with those of Freeman *et al.* (1993), but the reasons for this are unknown.

The final contaminant used in the slurry gavages was dioxin. All but the 1980 Poiger and Schlatter study used actual site contaminated soils; all had decreased bioavailability from the soils. Poiger and Schlatter also showed that the longer the dioxin was in contact with the soil, the less bioavailable the dioxin became. The 1984 McConnell *et al.* study results display the differences that specific site soils can have on bioavailability. The two soils had a significantly different effect on the LD<sub>50</sub> for guinea pigs as well as decreasing bioavailability when compared to corn oil gavage administration.

TABLE 11: RESULTS SUMMARY FOR SLURRY GAVAGE STUDIES

Test Substance	Results	Bioavailability	Reference
Dioxin contaminated soil	Contaminated soil was less bioavailable as compared to dioxin in acetone:vegetable oil or dioxin in alcohol:water. Spiked soil was less bioavailable as compared to dioxin in acetone:vegetable oil or dioxin in alcohol:water.	32%  56-71%	Bonaccorsi <i>et al.</i> , 1984.
PCB spiked soil	Spiked soil in gavage was more bioavailable than same spiked soil fed in diet.	80-90% (spiked soil dose/PCB in corn oil gavage)	Fries <i>et al.</i> , 1989. Fries <i>et al.</i> , 1981.
Sodium arsenate spiked soils (Male & Female)	(Spiked sandy soil, spiked clay soil vs. no soil, respectively) Spiked soils had little effect on bioavailability as compared to oral gavage with sodium arsenate. (All values are expressed as absolute percent bioavailability based on i.v. dosing.)	28, 23 vs. 29 % (male low dose group) 62, 64 vs. 79 % (male high dose group) 27, 21 vs. 24 % (female low dose group) 45, 46 vs. 41 % (female high dose group)	Griffin & Turck, 1991.
Dioxin contaminated soil	Contaminated soil increased AHH, P-450, & UDP glucuronyltransferase activity, as did dioxin in corn oil gavage.	approx. 50% as compared to dioxin in corn oil gavage (based on dioxin liver concentration)	Lucier <i>et al.</i> , 1986.

Dioxin contaminated soils (guinea pig)	Times Beach soil LD <sub>50</sub> = 7.15 µg/kg Minkler soil LD <sub>50</sub> = 5.50 µg/kg (Dioxin in corn oil gavage LD <sub>50</sub> = 1.75 µg/kg )	Decreased in contaminated soils as compared to dioxin in corn oil gavage	McConnell <i>et al.</i> , 1984.
Dioxin contaminated soil (rat)	Increased P-450 & AHH induction, to a lesser extent than dioxin in corn oil gavage. Liver concentrations of dioxin in contaminated soil & dioxin in corn oil gavage was 20.3 ppb & 40.8 ppb respectively.	Decreased in contaminated soil as compared to dioxin in corn oil gavage	McConnell <i>et al.</i> , 1984.
Dioxin spiked soil	Spiked soil with 10-15 hours contact - 24.1% dose in liver Spiked soil with 8 days contact - 16% dose in liver (Dioxin in ethanol gavage - 36.7% dose in liver) (Dioxin in activated carbon gavage - ≤0.07% dose in liver)	Decreased in spiked soil as compared to dioxin in ethanol gavage	Poiger & Schlatter, 1980.
Dioxin contaminated soil	Contaminated soil was less bioavailable as compared to corn oil gavage.	43% (contaminated soil gavage/dioxin in corn oil gavage (adjusted for approximate 30% nonabsorption of dioxin in corn oil gavage))	Shu <i>et al.</i> , 1988.
AHH = aryl hydrocarbon hydroxylase; PCB = polychlorinated biphenyls			

The results of the extracted materials study is found in Table 12. The extraction caused toxicity and reproductive effects. This type of study is useful for establishing that toxic chemicals are present and for beginning to identify them. However, it would be desirable to also know that the effect is seen in the presence of soil.

TABLE 12: RESULT SUMMARY FOR ORAL DOSING WITH EXTRACTED MATERIALS

Test Substance	Results	Results
Love Canal soil Extract	Mortality at high dose. Increased liver weight with hepatocyte hypertrophy. Decreased fetal birthweight; delayed ossification.	Silkworth <i>et al.</i> , 1986.

## BIOAVAILABILITY IN RISK ASSESSMENT

Bioavailability of chemicals represents a critical interface between the exposure and dose-response assessment steps in site-specific risk assessment. The exposure assessment estimates the chemical dose to which a person might be exposed through a given pathway. Estimates of chemical concentration in environmental media and estimates and assumptions about the parameters in the exposure pathway are required for this process. The dose-response assessment uses human epidemiological or experimental data when it is available, and more commonly toxicity data from laboratory animal studies to estimate the response at various doses. Except in those rare cases where both steps are based upon the identical exposure in humans (e.g. cancers associated with human drinking water consumption of arsenic), adjustments need to be made.

Broadly defined, bioavailability adjustments in risk assessment could encompass any differences between the environmental sample and the chemical form in the dose-response study or between the human in the risk assessment pathway and the species used in the dose-response study. Several methods are available to address these adjustments as briefly described below. Typically the lack of required information is the limiting factor.

### Bioavailability Adjustment Factors

The differences between the human risk assessment pathway and the dose-response study may be addressed using a relative BAF (Magee and Bradley, 1994). Limited descriptions of this method are found in guidance documents for Superfund risk assessment. Appendix A of the Risk Assessment Guidance for Superfund, Volume 1: Human Health Evaluation Manual (Part A) is titled "Adjustments for Absorption Efficiency" (EPA, 1989).

Bioavailability adjustments might be necessary in a site specific risk assessment for three reasons. First, the toxicity value may need to be expressed as a function of the absorbed dose. This is common when dealing with dermal exposures where the exposure estimates are expressed as the amount absorbed. Second, when the toxicity value for a chemical is based upon absorbed rather than administered dose, the exposure dose estimate will need to be

adjusted to an absorbed dose. Third, the medium of exposure on the site may be different from the medium used in the dose-response study. For instance, soil exposure is a common scenario in risk assessments, but there are no toxicity values based upon exposure to this media (EPA, 1989).

Adjustments for differences in media are calculated by first dividing the percent absorption of the contaminant from the soil by the percent absorption from the medium used in the dose-response study. This ratio is the BAF. The BAF is then multiplied by the exposure estimate, resulting in the adjusted exposure level. The adjusted exposure is comparable with the toxicity value of the chemical (EPA, 1989).

Bioavailability adjustment factors are a relatively simplistic approach. They typically address only the total amount absorbed in some time period rather than analyzing the effect on absorption kinetics. Their value arises because they do not require as detailed information as would be required for PBPK modeling. Therefore, BAFs can provide a reasonable first estimate of the impact of critical site-specific factors such as exposure to soil.

#### Physiologically Based Pharmacokinetic Modeling

A potentially stronger method to address the effect of differences in absorption is using physiologically based pharmacokinetic modeling. By developing descriptions of the absorption of the chemical in the study (e.g. dosing frequency, matrix, route, species etc.) from which the dose-response value was developed, the model can then estimate the alterations that would occur in subsequent pharmacokinetics (e.g. peak blood concentrations or metabolism). When the internal dose metric (e.g. metabolite concentration in the target tissue) that correlates with the toxicity is known, the impact of altered absorption can be estimated.

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